PATENT
Attorney Docket **GENE-035/09US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **D. MENDRICK** *et al.*	)	
	)	
Application No.: **09/917,800**	)	Group Art Unit: **1631**
	)	
Filed: **July 31, 2001**	)	Examiner: **Cheyne D. Ly**
	)	
For: **Molecular Toxicology Modeling**	)	

Mail Stop PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR ACCORDING THE FILING DATE
OF A TIMELY FILED RESPONSE

Sir:

It has been brought to our attention that our Amendment in response to the Office Action issued on June 6, 2005 for the above-referenced application, which we timely filed on December 6, 2005, has not been correctly entered by the Patent Office due to typographic errors in the Application Serial No. on Applicants' Amendment. The correct Serial No. of the present application is **09/917,800**. However, in our December 6, 2005 Amendment, the Serial No. was inadvertently typed as **10/917,800**. A typographic error was also made in the headings of the Amendment. Instead of showing "Application **09/917,800**" the heading reads "Application 10/152,319" which is a different patent application pending before the Patent Office. We believe it was due to these typographic errors that the Patent Office was unable to match the correct file with the submitted Amendment.

We have since corrected the typographic errors and hereby resubmit the December 6, 2005 Amendment (see Appendix A.) Since the December 6, 2005 Amendment were timely filed except for the typographic errors noted above, Applicants petition the Director of the USPTO to accord the same filing date to the present resubmitted Amendment. We enclose herein a copy of the postcard receipt of the filing of the Amendment and the originally filed Amendment with the USPTO date stamp (December 6, 2005) as evidence that the Amendments were timely filed in response to the Office Action (see Appendix B.)

PATENT
Attorney Docket **GENE-035/09US**
Application No. **09/917,800**

If there are any fees due in connection with the filing of this petition, please charge the fees to our Deposit Account No. 50-1283. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: January 5, 2006

Respectfully submitted,
Cooley Godward LLP

By _____
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FROM: Michael S. Tuscan **PHONE:** (202) 842-7802 **REPLY FAX:** (202) 842-7899

RE: Petition for According the Filing Date of a Timely Filed Response
Application No. 09/917,800

NUMBER OF PAGES, INCLUDING COVER PAGE: 40	Client Number: 071912-2108
Atty Dkt. No.: GENE-035/09US	Requestor #: 13247

MESSAGE:

I hereby certify that the below documents:

1. Petition for According the Filing Date of a Timely Filed Response(2 pgs.) with Authorization to Charge Deposit Account No. 50-1283;
2. Appendix A (Resubmitted Amendment and Reply Under 37 CFR § 1.111 (15 pgs.)); and
3. Appendix B (Copy of Amendment and Reply, Extension of Time and date-stamped postcard as filed 12/6/05 (19 pgs.))

were transmitted via facsimile to the U.S. Patent and Trademark Office on January 5, 2006.

Rayna R. Smith

12530 v1/DC

If you do not receive all of the pages, please call Rayna Smith at 202-842-7824 as soon as possible.

APPENDIX A

PATENT
Attorney Docket **GENE-035/09US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **D. MENDRICK** *et al.*
Application No.: **09/917,800**) Group Art Unit: **1631**
Filed: **July 31, 2001**) Examiner: **Cheyne D. Ly**
For: **Molecular Toxicology Modeling**

Mail Stop AMENDMENT
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AMENDMENT UNDER 37 C.F.R. § 1.111

This paper responds to the non-final Office Action dated June 6, 2005. A petition for a three-month extension of time is submitted herewith, extending the period from September 6, 2005 to December 6, 2005.

Applicants respectfully request reconsideration of this application in view of the following amendment and remarks.

Please amend the above-identified application as follows:

Amendments to the Specification begins on page 3 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 4 of this paper.

Remarks/Arguments begin on page 9 of this paper.

Amendments to the specification

Please amend the specification as follows:

Please replace the paragraph beginning on page 23, line 28, ending on page 24, line 6, with the following:

The sequences of the expression marker genes of Tables 1-2 are in the public databases. Table 1 provides the GenBank Accession Number for each of the sequences ~~(see wwww.ncbi.nlm.nih.gov/)~~. The sequences of the genes in GenBank are expressly herein incorporated by reference in their entirety as of the filing date of this application, as are related sequences, for instance, sequences from the same gene of different lengths, variant sequences, polymorphic sequences, genomic sequence of the genes and related sequences from different species, including the human counterparts, where appropriate. These sequences may be used in the methods of the invention or may be used to produce the probes and arrays of the invention. In some embodiments, the genes in Tables 1-3 that correspond to the genes or fragments previously associated with a toxic response may be excluded from the Tables.

Please replace the paragraph on page 43, lines 15-25, with the following:

The second approach used has been described in U.S. Provisional Application ~~60/_____~~ 60/263,161, using this approach all 527 genes and/or EST were used to predict toxic from non-toxic samples with greater than 94% accuracy when 15 components are used. Although using the first fifteen components provided a preferred model, other variations of this method can provide adequate predictive ability. These include selective inclusion of components via agglomerate, divisive, or random approaches. Also the use of these composite variables in logistic regression to determine classification of samples can also be accomplished with linear discriminate analysis, neural or Bayesian networks, or other forms of regression to determine analysis, neural or Bayesian networks, or other forms of regression and classification based on categorical or continual dependent and independent variables

Amendments to the claims

In the claims:

Claims 1-91(Canceled)

92. (currently amended) A method of predicting for the hepatoxicity of a test compound, comprising:

(a) preparing a gene expression profile of at least ten genes from a liver tissue or liver cell sample exposed to the test compound; and

(b) comparing the expression levels of said at least ten genes from the gene expression profile to a database comprising the gene expression levels of said at least ten genes derived from liver tissue or liver cell samples that have been exposed to at least one known ~~hepatoxin~~ hepatotoxin, wherein said at least ten genes are selected from the ~~genes~~ gene sequences listed in any one of Tables 3A-3S, thereby predicting for the hepatoxicity of the test compound.

93. (previously presented) A method of claim 92, wherein the gene expression profile prepared from the liver tissue or liver cell sample comprises the level of expression for at least 100 genes.

94. (previously presented) A method of claim 92, wherein expression levels for said at least ten genes from the gene expression profile are compared to Toxic Mean and/or NonToxic Mean values in a database comprising any one of Tables 3A-3S.

95. (previously presented) A method of claim 94, wherein the level of expression for each gene is normalized prior to comparison.

96. (previously presented) A method of claim 92, wherein the database comprises all of the data in any one of Tables 3A-3S.

97. (previously presented) The method of claim 92, wherein the expression levels of at least 15 genes are compared to the database.

98. (previously presented) The method of claim 92, wherein the expression levels of at least 20 genes are compared to the database.

99. (previously presented) The method of claim 92, wherein the expression levels of at least 25 genes are compared to the database.

100. (previously presented) The method of claim 92, wherein the expression levels of at least 30 genes are compared to the database.

101. (previously presented) The method of claim 92, wherein the expression levels of at least 50 genes are compared to the database.

102. (previously presented) The method of claim 92 wherein the expression levels of at least 75 genes are compared to the database.

103. (previously presented) The method of claim 92, wherein the expression levels of at least 100 genes are compared to the database.

104. (currently amended) The method of claim 92, wherein the liver cell or liver tissue sample is exposed to the test compound *in vivo* and the liver cell or liver tissue samples from which database information is derived are exposed to the at least one known ~~hepatoxin~~ hepatotoxin *in vivo*.

105. (previously presented) A method of claim 104, wherein the hepatoxicity is associated with at least one liver disease pathology selected from the group consisting of liver damage induced by hepatitis, liver damage induced by NSAIDS, liver necrosis with fatty liver, liver necrosis without fatty liver and liver damage induced by compounds that form protein adducts.

106. (currently amended) A method of claim 92, wherein the ~~hepatoxin~~ hepatotoxin is selected from the group consisting of amitryptiline, ANIT, acetaminophen, carbon tetrachloride, cyproterone acetate, diclofenac, estradiol, indomethacin, valproate, and WY-14643.

107. (previously presented) A method of claim 92, wherein the gene expression profile is produced by hybridization of nucleic acids to a microarray.

108. (previously presented) A method of claim 92, wherein the liver cell or liver tissue sample is a rat liver cell or rat liver tissue sample.

109. (currently amended) A method of claim 92, wherein said ~~the~~ selected genes ~~in Tables 3A-3S~~ are rat genes.

110. (previously presented) A method of claim 104, wherein the hepatoxicity is liver necrosis.

111. (currently amended) A method of predicting for the liver toxicity of a test compound, comprising:

(a) preparing a gene expression profile of at least ten genes from a liver tissue or liver cell sample exposed to the test compound; and

(b) comparing the expression levels of said at least ten genes from the gene expression profile to a database comprising the gene expression levels of said at least ten genes derived from liver tissue or liver cell samples that have been exposed to at least one known liver toxin, wherein said at least ten genes are selected from the ~~genes~~ gene sequences listed in any one of Tables 3A-3S, thereby predicting for the liver toxicity of the test compound.

112. (previously presented) A method of claim 111, wherein the gene expression profile prepared from the liver tissue or liver cell sample comprises the level of expression for at least 100 genes.

113. (previously presented) A method of claim 111, wherein expression levels for said at least ten genes from the gene expression profile are compared to Toxic Mean and/or NonToxic Mean values in a database comprising Tables 3A-3S.

114. (previously presented) A method of claim 111, wherein the level of expression

for each gene is normalized prior to comparison.

115. (previously presented) A method of claim 111, wherein the database comprises all of the data in any one of Tables 3A-3S.

116. (previously presented) The method of claim 111, wherein the expression levels of at least 15 genes are compared to the database.

117. (previously presented) The method of claim 111, wherein the expression levels of at least 20 genes are compared to the database.

118. (previously presented) The method of claim 111, wherein the expression levels of at least 25 genes are compared to the database.

119. (previously presented) The method of claim 111, wherein the expression levels of at least 30 genes are compared to the database.

120. (previously presented) The method of claim 111, wherein the expression levels of at least 50 genes are compared to the database.

121. (previously presented) The method of claim 111, wherein the expression levels of at least 75 genes are compared to the database.

122. (previously presented) The method of claim 111, wherein the expression levels of at least 100 genes are compared to the database.

123. (previously presented) The method of claim 111 wherein the liver cell or liver tissue sample is exposed to the compound *in vivo* and the liver cell or liver tissue samples from which database information is derived are exposed to the at least one known liver toxin *in vivo*.

124. (previously presented) A method of claim 123, wherein the liver toxicity is associated with at least one liver disease pathology selected from the group consisting of liver

damage induced by hepatitis, liver damage induced by NSAIDS, liver necrosis with fatty liver, liver necrosis without fatty liver and liver damage induced by compounds that form protein adducts.

125. (previously presented) A method of claim 123, wherein the liver toxin is selected from the group consisting of amitryptiline, ANIT, acetaminophen, carbon tetrachloride, cyproterone acetate, diclofenac, estradiol, indomethacin, valproate, and WY-14643.

126. (previously presented) A method of claim 111, wherein the gene expression profile is produced by hybridization of nucleic acids to a microarray.

127. (previously presented) A method of claim 111, wherein the liver cell or liver tissue sample is a rat liver cell or rat liver tissue sample.

128. (currently amended) A method of claim 111, wherein said ~~the~~ selected genes ~~in Tables 3A-3S~~ are rat genes.

129. (previously presented) A method of claim 123 wherein the liver toxicity is liver necrosis.

REMARKS

Applicants respectfully submit that no prohibited new matter has been introduced by the foregoing amendments. Support for the amendments to the claims can be found in the original claims, figures and throughout the specification as originally filed. Claims 92 and 111 have been amended to replace the word "genes" with "gene sequences." Support for the amendments can be found at page 23, line 28 to page 24, line 14 of the specification. Support for the correction of the typographic error "hepatoxin" can be found at page 1, line 28 of the specification. The amendments to claims 109 and 128 merely provide proper antecedent basis for the further dependent claim limitations. Claims 92-129 are pending before the Examiner for examination.

The Office Action dated June 6, 2005 has been carefully reviewed and the following reply is made in response thereto. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Summary of Office Action

1. Claims 92-129 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.
2. Claims 92-129 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.
3. Claims 109 and 128 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter.
4. Claims 92, 106 and 111 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Farr *et al.* (US Patent 5,811,231).
5. Claims 92, 97-101, 111 and 116-120 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231).
6. Claims 92, 107, 111 and 126 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231) in combination of Lashkari *et al.* (PNAS, Vol. 94, pages 13057-13062, 1997).

Specification Objections

The Examiner objects to the specification, allegedly because it contains an embedded hyperlink and/or other form of browser-executable code (Page 23, Line 30) and requests the deletion of the embedded hyperlink in accordance with MPEP § 608.01. Without acquiescing to the objection, the specification has been amended to remove the hyperlink.

The Examiner also objects to the specification on page 43, where the application number of a U.S. Provisional Application is incomplete. In response, Applicants have provided the missing number. In view of the amendments, the Examiner's objections are moot.

Claim Rejections-35 U.S.C. § 112, First Paragraph (Lack of Enablement)

The Examiner has rejected claims 92-129 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in a way to enable one skilled in the art to make or use the claimed invention.

More specifically, the Examiner alleges that the claimed method requires the comparison of a gene expression profile from a liver tissue or liver cell sample exposed to a test compound to a database. The Examiner evidently assumes that the database has been populated with data generated from liver, heart, kidneys, testes, and brain harvested from Sprague-Dawley rats exposed to a known toxin. The Examiner correctly contends that the specification teaches that the tissue types collected are from liver, heart, kidneys, testes, and brain but then incorrectly assumes that the data in Tables 3A-3S are from tissues other than liver. The Examiner concludes that one skilled in the art would require undue experimentation to be able to predict hepatoxicity or liver toxicity when the comparison is performed with a database comprising expression data from various organs such as liver, heart, kidneys, testes, and brain.

Applicants respectfully submit that the Examiner's characterization of the data in Tables 3A-3S as gene expression data from various organs rather than the liver is incorrect. As explained in detail in the specification, all the genes disclosed in the Tables are pertinent to one or more toxic responses of the liver as claimed in the present invention. As clearly stated in the instant application, "the genes and gene expression information...provided in Tables 1-3, may be used to predict at least one toxic effect, including the hepatotoxicity of a test or unknown compound. (page 15, lines 17-19) [Emphasis added.] In other words, each gene in the Tables 3A-3S is differentially expressed in liver cells or liver tissues after exposure to at

least one hepatotoxin. It is thus clear that the genes in Tables 3A-3S are by no means randomly selected from various organs such as liver, heart, kidneys, testes, and brain as asserted by the Examiner. Rather, these are genes differentially expressed in liver tissues or liver cell samples when exposed to a toxic compound. The models of Tables 3A-3S are thus specific to liver toxicity as opposed to the toxicity of other organ tissues.

For these reasons, Applicants respectfully submit that the specification provides sufficient disclosure that the differential expression is specific to liver toxicity or hepatoxicity for the liver as opposed to the toxicity of other organ tissues in the experiment. Thus, one skilled in the art would have recognized that the comparison of gene expression profiles was performed between liver tissues as taught in the specification rather than liver and other organs.

To doubt the operability of the invention, the Examiner has the initial burden to provide evidence to the contrary. It is well settled in the patent case law that a specification disclosure that contains a teaching of the manner and process of making and using the invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Further, the burden is on the Examiner to come forth with evidence to establish a prima facie case of non-enablement. *Ex parte Hitzeman*, 9 U.S.P.Q. 2d 1801, 1822 (Pat. Off. Bd. App. 1988); *In Re Armbruster*, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975); *In re Marzocchi*, 169 U.S.P.Q. at 370. While Applicants have provided ample evidence in the specification to show the methods disclosed in the present invention can successfully predict liver toxicity of test compounds, the Examiner has not provided any scientific evidence whatsoever to show that one skilled in the art would undergo undue experimentation to practice the present invention. Applicants therefore respectfully request the rejection be withdrawn.

The Examiner further contends that Table 1 does not comprise the identities of the metabolic pathways and that Applicants do not provide any disclosure as to whether the listed genes are specific for the metabolic pathways in the liver, or if said genes function specifically in the liver that are involved in hepatoxicity or liver toxicity. Applicants respectfully submit that in all the pending claims, no claim is drawn to a method of predicting the cellular pathways. Since the subject matter of cellular pathways is not claimed, the Examiner's

rejection is irrelevant to the pending claims. Applicants respectfully request that the rejection be withdrawn.

The Examiner further states that claims 105 and 124 recite specific disease pathologies that are predicted with the claimed methods. The Examiner then asserts that Applicants do not disclose whether the comparison is performed with normal liver tissues and liver tissues having the respective liver disease pathologies.

Applicants respectfully submit that claims 105 and 124 are dependent from claims 92 and 111, respectively. Both claims 92 and 111 recite a method of predicting for hepatoxicity of a test compound by preparing a gene expression profile from a liver tissue or liver cell sample exposed to the test compound. One of skill in the art would have recognized that the liver tissues or liver cells described in claims 92 and 111 are normal liver tissues before they are exposed to the test compound or known hepatotoxin. As an example, a hepatotoxin such as CCl_4 is known to induce hepatocellular damage or death. A gene expression profile derived from liver tissue exposed to CCl_4 carries the characteristic hepatocellular damage gene expression pattern. This pattern, in part, corresponds to the model of Tables 3I-3J. By comparing a gene expression profile of a liver tissue exposed to a test compound with a database of Tables 3I-3J produced from liver tissue exposed to CCl_4, one of skill in the art can predict whether the test agent induces hepatocellular damage or death. Accordingly, withdrawal of the pending rejection is requested.

Claim Rejections-35 U.S.C. § 112, First Paragraph (Lack of Written Description)

Claims 92-129 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention. More specifically, the Examiner contends that Claims 92-129 encompass "the genes in any one of Tables 3A-3S". However, Table 1 only discloses gene sequences with specific SEQ ID NOs. Therefore, the specification provides insufficient written description to support the genus encompassed by these claims.

Without acquiescing to the grounds of the Examiner's rejection, claims 60 and 80 have been amended to clarify that the genes are selected from the gene sequences listed in any one of Tables 3A-3S as correlated to the representative sequences of Table 1 and teachings of the specification. Applicants respectfully submit that the skilled artisan knows

the detailed chemical structure of the encompassed gene sequences as these sequences are all known sequences in the art and are specifically provided in the sequence listing submitted with the instant application. Furthermore, Applicants respectfully submit the facts in the present case differ significantly from those in the cited case law. *University of California v. Eli Lilly*, 43 U.S.P.Q. 2d 1398, describes the Federal Circuit's current view on patentability of cDNAs. Lilly cloned the rat insulin gene and described methods for isolating human cDNA based on the isolation of the rat insulin gene and known human insulin sequences. The court stated that the discovery of a single gene for rat insulin could not describe the entire group of vertebrate insulin DNA, or mammalian insulin DNA, as was claimed. *Amgen*, 18 U.S.P.Q. 2d 1016, concerned claims to a purified and isolated naturally occurring gene. The court held that a gene cannot be claimed until it is fully defined, *e.g.*, by determination of its nucleic acid sequence.

In contrast to the facts of *Lilly* and *Amgen*, the present invention includes methods of predicting for the hepatoxicity of a test compound by preparing a gene expression profile of at least ten genes from a liver tissue or liver cell sample exposed to the test compound. The claims are not directed to gene sequences that have not been disclosed as in *Lilly* and *Amgen*. Rather, the method of the present invention may be used to prepare gene expression profiles and compare those profiles to a database disclosed in the present application, wherein the nucleotide sequence for each and every gene in the database (one of Tables 3A-3S) is disclosed in the present application and is publicly available in GenBank. Applicants respectfully remind the Examiner that each "Identifier" in Tables 3A-3S corresponds to a GenBank Accession No. and SEQ ID NO. as correlated and set forth in Table 1.

As for the Examiner's concern of incorporation of essential material into the specification, Applicants respectfully submit that all of the gene sequences referred to by their GLGC ID in Tables 3A-3S are available from the GeneBank and thus are in public possession. Further, each sequence corresponding to each GenBank Accession No. is provided in the sequence listing which is part of the originally filed application (see Table 1). Therefore, Applicants have met the requirements of the first paragraph of Section 112 and respectfully request that this rejection be withdrawn.[1]

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1 Applicants note that sequences in GenBank are publicly available. Further, it has been long established that an Applicant need not provide in a patent application what is already known in the art. *Hybritech Inc. v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Claim Rejections-35 U.S.C. § 112, Second Paragraph

Claims 109 and 128 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, the Examiner contends that claims 109 and 108 recite the limitation of "the genes in Tables 3A-3S are rat genes" whereas Table 1 comprises sequences from R. norvegicus (rat), M. musculus (mouse), and unknown and the data in Tables 3A-3S are directed to the sequences listed in Table 1.

Applicants respectfully submit that there is no inconsistency in identifying the genes in Tables 3A-3S and Table 1. The assays described in the specification were all done in Sprague-Dawley rats and thus are rat genes. Although each of the genes in Tables 3A-3S correspond to a sequence listed in Table 1, Table 1 does not comprise only gene sequences from Tables 3A-3S. Therefore, Table 1 may comprise sequences from R. norvegicus (rat), M. musculus (mouse), or other species. Because claims 109 and 128, as amended, are not vague and indefinite, Applicants respectfully request withdrawal of this rejection.

Claim Rejections-35 U.S.C. § 102(b)

Claims 92, 106 and 111 are rejected under 35 U.S.C. 102(b) as being anticipated by Farr *et al.* (US Patent 5,811,231). According to the Examiner, Farr *et al.* describe a method for determining and characterizing the toxicity (predict) of a compound in terms of the damage it causes within the cell. The method of Farr *et al.* comprises exposing cells to a compound and creating an inducting profile (expression profile). As stated by the Examiner, Farr *et al.* also disclose a database of gene expression profiles comprising the GADD153, GADD45, HSP70, UGT, DNA pol, EH, CYP2E1, ALDH1 and ALDH2, IL-3, and IL-6 genes. The Examiner the asserts that the genes discloses by Farr *et al.* represents the at least 10 genes in Tables 3A-3S of the instant Application which are identified by the GLGC ID NOs: 351 (GADD45), 488 (CYP2E1), 1475 (HSP70), 1598 (GADD153), 2744 (UGT), 6615 (alcohol dehydrogenase), 14103 (EH), 14465 (DNA pol), and 20799 (IL3 and IL6). Applicants respectfully traverse.

For a reference to anticipate the claimed invention under 35 U.S.C. §102, the reference must describe the invention such that "each and every limitation is found either expressly or inherently" within it. *Transclean Corp. B. Bridgewood Services, Inc.*, 290 F.3d 1364, 1370, 62 USPQ2d 1865, 1869 (Fed. Cir. 2002) (citations omitted); see Manual of Patent Examining Procedure, section 2131 (8th ed. 2004) ("MPEP") ("to anticipate a claim,

the reference must teach every element of the claim").

Claims 92 and 111 recite in part "wherein said at least ten genes...in any one of Tables 3A-3S." Applicants submit that the 10 genes recited in the Office Action as having been disclosed in Farr *et al.* do not correspond to at least 10 genes from any one of Tables 3A-3S as required by the pending claims. As evidenced by the plain language of claims 92 and 111, the database as claimed in the instant methods comprises gene expression levels for "at least ten genes...in any one of Tables 3A-3S." [Emphasis added.] As such, the comparison step of claims 92 and 111 is to a set of genes from a single liver toxicity model of any one of Tables 3A-3S as each of these tables discloses a single liver toxicity model. In other words, the comparison step of claims 92 and 111 is not to a set of at least 10 genes randomly selected from different models. Respectfully, the 10 genes recited in the Office Action from Farr *et al.* do not correspond to at least 10 genes from any one of Tables 3A-3S as claimed. Accordingly, Farr *et al.* cannot anticipate any of the pending claims. The pending rejection under 35 U.S.C. § 102(b) should be withdrawn.

Claim Rejections-35 U.S.C. § 103(a)

Claims 92, 97-101, 111, and 116-120 are rejected under 35 U.S.C. §103(a) as being unpatentable over Farr et al. (US patent 5,811,231). Applicants respectfully traverse this rejection. Applicants first reiterate that in order for a reference to render a claim obvious under § 103, it must teach or suggest all of the elements of that claim. However, as described in the preceding section, Farr does not teach or suggest the at least 10 genes from "any one of Tables 3A-3S," as required by all of claims 92, 97-101, 111, and 116-120. No other reference was cited to correct this deficiency. Therefore, the Examiner has failed to provide a prima facie case of obviousness, and Applicants request the withdrawal of this rejection.

Claims 92, 107, 111 and 126 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231) in combination of Lashkari *et al.* (PNAS, Vol. 94, pages 13057-13062, 1997). This rejection is also respectfully traversed.

With respect to the primary reference Farr *et al.*, the Examiner is directed to the discussions of the §102 rejection presented above. As indicated, Farr *et al.* do not disclose or suggest that the at least 10 genes to be compared are selected from any one of Tables 3A-3S.

The other cited reference, Lashkari *et al.* do not provide what Farr lacks.

Lashkari is limited to a disclosure of gene expression patterns of the yeast genome. Lashkari *et al.* do not discuss any method remotely related to Applicant's claimed method of predicting for the hepatoxicity of a compound using liver tissues or liver cell samples, nor does it discuss databases comprising the gene expression levels derived from liver tissue or liver cell samples in any context.

Accordingly, even if these references were properly combined (which Applicants do not concede), the combination of Farr and Lashkari does not provide Applicant's claimed method predicting for the hepatoxicity of a compound with liver tissues or liver cell samples because neither reference discloses or suggests the important step of selecting the at least 10 genes from any one of Tables 3A-3S. Applicants respectfully request that the §103(a) rejection be withdrawn.

Conclusion

Applicant respectfully requests reconsideration of the subject application in view of the amendments to the claims and the above remarks. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this amendment, the Examiner is requested to contact the Applicant's undersigned representative.

If there are any fees due in connection with the filing of this amendment, please charge the fees to our Deposit Account No. 50-1283. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: January 5, 2005

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APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PLEASE DATE STAMP AND RETURN TO SHOW RECEIPT OF:

In re Application of: Donna L. MENDRICK et al.
Application No. 10/917,800 Filed: July 31, 2001

For: **MOLECULAR TOXICOLOGY MODELING**

1. Transmittal of Response (2 pgs.);
2. Petition for Extension of Time (3 mths.) (1 pg.);
3. Amendment & Reply (15 pgs.); and
4. Return Receipt Postcard.

Dated: December 6, 2005
Attorney Docket No.: 044921-5038
Atty/Secy: MST/HL/rrs

11653 v1/DC

Attorney Docket No. 044921-5038 PATENT

DEC 06 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Donna L. MENDRICK et al. Examiner: C. D. Ly

Serial No.: ~~10/917,800~~ 10/152,319 Art Unit: 1631

Filed: July 31, 2001

For: MOLECULAR TOXICOLOGY MODELING

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The following extension of time is requested to respond to the Non-Final Office Action dated June 6, 2005, 3 months to December 6, 2005; the extension fee is:

[] $510.00 [X] $1020.00

[] The shortened statutory period has been reset by an Advisory Action dated

[] An extension fee in the amount of $ _____ is enclosed.

[X] Charge $1020.00 to Deposit Account No. 50-1283.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283. This paper is submitted in duplicate.

Dated: 12-6-05

Respectfully submitted,
COOLEY GODWARD LLP

By: _____
Michael S. Tuscan
Reg. No. 43,210

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Attorney Docket No.: 44921-5038 PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Donna L. MENDRICK et al. Examiner: C. D. Ly

Serial No.: ~~10/917,800~~ 10/152,319 Art Unit: 1631

Filed: July 31, 2001

For: **MOLECULAR TOXICOLOGY MODELING**

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF RESPONSE

Enclosed are the following documents in response to the Office Action dated June 6, 2005, for the above-identified application:

[X] Amendment and Reply (15 pgs.);
[X] Petition for Extension of Time (3 months); and
[X] Return receipt postcard.

The fee has been calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY FILED.	EXTRA CLAIMS	RATE	FEE
Total Claims	38	-38=	0	x $50.00	$0.00
Independent Claims	2	-3=	0	x $200.00	$0.00
If multiple dependent claims are presented, add $360.00					
Total Amendment Fee					$0.00
Other fees: (specify) Extension of Time (3 mth.)					$1020.00
If small entity status is applicable, subtract 50% of Total Amendment Fee					
TOTAL FEE DUE					$1020.00

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Respectfully submitted,
COOLEY GODWARD LLP

Dated: 1-6-05

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12026 v1/DC

PATENT
Attorney Docket 044921-5038

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **D. MENDRICK *et al.***

Application No.: ~~10/917,800~~ 10/152,319 Group Art Unit: **1631**

Filed: **July 31, 2001** Examiner: **Cheyne D. Ly**

For: **Molecular Toxicology Modeling**

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. § 1.111

This paper responds to the non-final Office Action dated June 6, 2005. A petition for a three-month extension of time is submitted herewith, extending the period from September 6, 2005 to December 6, 2005.

Applicants respectfully request reconsideration of this application in view of the following amendment and remarks.

Please amend the above-identified application as follows:

Amendments to the Specification begins on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 8 of this paper.

Amendments to the specification

Please amend the specification as follows:

Please replace the paragraph beginning on page 23, line 28, ending on page 24, line 6, with the following:

The sequences of the expression marker genes of Tables 1-2 are in the public databases. Table 1 provides the GenBank Accession Number for each of the sequences (~~see wwww.nebi.nlm.nih.gov/~~). The sequences of the genes in GenBank are expressly herein incorporated by reference in their entirety as of the filing date of this application, as are related sequences, for instance, sequences from the same gene of different lengths, variant sequences, polymorphic sequences, genomic sequence of the genes and related sequences from different species, including the human counterparts, where appropriate. These sequences may be used in the methods of the invention or may be used to produce the probes and arrays of the invention. In some embodiments, the genes in Tables 1-3 that correspond to the genes or fragments previously associated with a toxic response may be excluded from the Tables.

Please replace the paragraph on page 43, lines 15-25, with the following:

The second approach used has been described in U.S. Provisional Application ~~60/_____~~ 60/263,161, using this approach all 527 genes and/or EST were used to predict toxic from non-toxic samples with greater than 94% accuracy when 15 components are used. Although using the first fifteen components provided a preferred model, other variations of this method can provide adequate predictive ability. These include selective inclusion of components via agglomerate, divisive, or random approaches. Also the use of these composite variables in logistic regression to determine classification of samples can also be accomplished with linear discriminate analysis, neural or Bayesian networks, or other forms of regression to determine analysis, neural or Bayesian networks, or other forms of regression and classification based on categorical or continual dependent and independent variables

Amendments to the claims

In the claims:

Claims 1-91(Canceled)

92. (currently amended) A method of predicting for the hepatoxicity of a test compound, comprising:

(a) preparing a gene expression profile of at least ten genes from a liver tissue or liver cell sample exposed to the test compound; and

(b) comparing the expression levels of said at least ten genes from the gene expression profile to a database comprising the gene expression levels of said at least ten genes derived from liver tissue or liver cell samples that have been exposed to at least one known ~~hepatoxin~~ hepatotoxin, wherein said at least ten genes are selected from the genes gene sequences listed in any one of Tables 3A-3S, thereby predicting for the hepatoxicity of the test compound.

93. (previously presented) A method of claim 92, wherein the gene expression profile prepared from the liver tissue or liver cell sample comprises the level of expression for at least 100 genes.

94. (previously presented) A method of claim 92, wherein expression levels for said at least ten genes from the gene expression profile are compared to Toxic Mean and/or NonToxic Mean values in a database comprising any one of Tables 3A-3S.

95. (previously presented) A method of claim 94, wherein the level of expression for each gene is normalized prior to comparison.

96. (previously presented) A method of claim 92, wherein the database comprises all of the data in any one of Tables 3A-3S.

97. (previously presented) The method of claim 92, wherein the expression levels of at least 15 genes are compared to the database.

98. (previously presented) The method of claim 92, wherein the expression levels of at least 20 genes are compared to the database.

99. (previously presented) The method of claim 92, wherein the expression levels of at least 25 genes are compared to the database.

100. (previously presented) The method of claim 92, wherein the expression levels of at least 30 genes are compared to the database.

101. (previously presented) The method of claim 92, wherein the expression levels of at least 50 genes are compared to the database.

102. (previously presented) The method of claim 92 wherein the expression levels of at least 75 genes are compared to the database.

103. (previously presented) The method of claim 92, wherein the expression levels of at least 100 genes are compared to the database.

104. (currently amended) The method of claim 92, wherein the liver cell or liver tissue sample is exposed to the test compound *in vivo* and the liver cell or liver tissue samples from which database information is derived are exposed to the at least one known ~~hepatoxin~~ hepatotoxin *in vivo*.

105. (previously presented) A method of claim 104, wherein the hepatoxicity is associated with at least one liver disease pathology selected from the group consisting of liver damage induced by hepatitis, liver damage induced by NSAIDS, liver necrosis with fatty liver, liver necrosis without fatty liver and liver damage induced by compounds that form protein adducts.

106. (currently amended) A method of claim 92, wherein the ~~hepatoxin~~ hepatotoxin is selected from the group consisting of amitryptiline, ANIT, acetaminophen, carbon tetrachloride, cyproterone acetate, diclofenac, estradiol, indomethacin, valproate, and WY-14643.

107. (previously presented) A method of claim 92, wherein the gene expression profile is produced by hybridization of nucleic acids to a microarray.

108. (previously presented) A method of claim 92, wherein the liver cell or liver tissue sample is a rat liver cell or rat liver tissue sample.

109. (currently amended) A method of claim 92, wherein said ~~the~~ selected genes ~~in Tables 3A-3S~~ are rat genes.

110. (previously presented) A method of claim 104, wherein the hepatoxicity is liver necrosis.

111. (currently amended) A method of predicting for the liver toxicity of a test compound, comprising:

(a) preparing a gene expression profile of at least ten genes from a liver tissue or liver cell sample exposed to the test compound; and

(b) comparing the expression levels of said at least ten genes from the gene expression profile to a database comprising the gene expression levels of said at least ten genes derived from liver tissue or liver cell samples that have been exposed to at least one known liver toxin, wherein said at least ten genes are selected from the ~~genes~~ gene sequences listed in any one of Tables 3A-3S, thereby predicting for the liver toxicity of the test compound.

112. (previously presented) A method of claim 111, wherein the gene expression profile prepared from the liver tissue or liver cell sample comprises the level of expression for at least 100 genes.

113. (previously presented) A method of claim 111, wherein expression levels for said at least ten genes from the gene expression profile are compared to Toxic Mean and/or NonToxic Mean values in a database comprising Tables 3A-3S.

114. (previously presented) A method of claim 111, wherein the level of expression

for each gene is normalized prior to comparison.

115. (previously presented) A method of claim 111, wherein the database comprises all of the data in any one of Tables 3A-3S.

116. (previously presented) The method of claim 111, wherein the expression levels of at least 15 genes are compared to the database.

117. (previously presented) The method of claim 111, wherein the expression levels of at least 20 genes are compared to the database.

118. (previously presented) The method of claim 111, wherein the expression levels of at least 25 genes are compared to the database.

119. (previously presented) The method of claim 111, wherein the expression levels of at least 30 genes are compared to the database.

120. (previously presented) The method of claim 111, wherein the expression levels of at least 50 genes are compared to the database.

121. (previously presented) The method of claim 111, wherein the expression levels of at least 75 genes are compared to the database.

122. (previously presented) The method of claim 111, wherein the expression levels of at least 100 genes are compared to the database.

123. (previously presented) The method of claim 111 wherein the liver cell or liver tissue sample is exposed to the compound *in vivo* and the liver cell or liver tissue samples from which database information is derived are exposed to the at least one known liver toxin *in vivo*.

124. (previously presented) A method of claim 123, wherein the liver toxicity is associated with at least one liver disease pathology selected from the group consisting of liver

damage induced by hepatitis, liver damage induced by NSAIDS, liver necrosis with fatty liver, liver necrosis without fatty liver and liver damage induced by compounds that form protein adducts.

125. (previously presented) A method of claim 123, wherein the liver toxin is selected from the group consisting of amitryptiline, ANIT, acetaminophen, carbon tetrachloride, cyproterone acetate, diclofenac, estradiol, indomethacin, valproate, and WY-14643.

126. (previously presented) A method of claim 111, wherein the gene expression profile is produced by hybridization of nucleic acids to a microarray.

127. (previously presented) A method of claim 111, wherein the liver cell or liver tissue sample is a rat liver cell or rat liver tissue sample.

128. (currently amended) A method of claim 111, wherein said ~~the~~ selected genes ~~in Tables 3A-3S~~ are rat genes.

129. (previously presented) A method of claim 123 wherein the liver toxicity is liver necrosis.

REMARKS

Applicants respectfully submit that no prohibited new matter has been introduced by the foregoing amendments. Support for the amendments to the claims can be found in the original claims, figures and throughout the specification as originally filed. Claims 92 and 111 have been amended to replace the word "genes" with "gene sequences." Support for the amendments can be found at page 23, line 28 to page 24, line 14 of the specification. Support for the correction of the typographic error "hepatoxin" can be found at page 1, line 28 of the specification. The amendments to claims 109 and 128 merely provide proper antecedent basis for the further dependent claim limitations. Claims 92-129 are pending before the Examiner for examination.

The Office Action dated June 6, 2005 has been carefully reviewed and the following reply is made in response thereto. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Summary of Office Action

1. Claims 92-129 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

2. Claims 92-129 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

3. Claims 109 and 128 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter.

4. Claims 92, 106 and 111 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Farr *et al.* (US Patent 5,811,231).

5. Claims 92, 97-101, 111 and 116-120 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231).

6. Claims 92, 107, 111 and 126 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231) in combination of Lashkari *et al.* (PNAS, Vol. 94, pages 13057-13062, 1997).

Specification Objections

The Examiner objects to the specification, allegedly because it contains an embedded hyperlink and/or other form of browser-executable code (Page 23, Line 30) and requests the deletion of the embedded hyperlink in accordance with MPEP § 608.01. Without acquiescing to the objection, the specification has been amended to remove the hyperlink.

The Examiner also objects to the specification on page 43, where the application number of a U.S. Provisional Application is incomplete. In response, Applicants have provided the missing number. In view of the amendments, the Examiner's objections are moot.

Claim Rejections-35 U.S.C. § 112, First Paragraph (Lack of Enablement)

The Examiner has rejected claims 92-129 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in a way to enable one skilled in the art to make or use the claimed invention.

More specifically, the Examiner alleges that the claimed method requires the comparison of a gene expression profile from a liver tissue or liver cell sample exposed to a test compound to a database. The Examiner evidently assumes that the database has been populated with data generated from liver, heart, kidneys, testes, and brain harvested from Sprague-Dawley rats exposed to a known toxin. The Examiner correctly contends that the specification teaches that the tissue types collected are from liver, heart, kidneys, testes, and brain but then incorrectly assumes that the data in Tables 3A-3S are from tissues other than liver. The Examiner concludes that one skilled in the art would require undue experimentation to be able to predict hepatoxicity or liver toxicity when the comparison is performed with a database comprising expression data from various organs such as liver, heart, kidneys, testes, and brain.

Applicants respectfully submit that the Examiner's characterization of the data in Tables 3A-3S as gene expression data from various organs rather than the liver is incorrect. As explained in detail in the specification, all the genes disclosed in the Tables are pertinent to one or more toxic responses of the liver as claimed in the present invention. As clearly stated in the instant application, "the genes and gene expression information...provided in Tables 1-3, may be used to predict at least one toxic effect, including the hepatotoxicity of a test or unknown compound. (page 15, lines 17-19) [Emphasis added.] In other words, each gene in the Tables 3A-3S is differentially expressed in liver cells or liver tissues after exposure to at

least one hepatotoxin. It is thus clear that the genes in Tables 3A-3S are by no means randomly selected from various organs such as liver, heart, kidneys, testes, and brain as asserted by the Examiner. Rather, these are genes differentially expressed in liver tissues or liver cell samples when exposed to a toxic compound. The models of Tables 3A-3S are thus specific to liver toxicity as opposed to the toxicity of other organ tissues.

For these reasons, Applicants respectfully submit that the specification provides sufficient disclosure that the differential expression is specific to liver toxicity or hepatoxicity for the liver as opposed to the toxicity of other organ tissues in the experiment. Thus, one skilled in the art would have recognized that the comparison of gene expression profiles was performed between liver tissues as taught in the specification rather than liver and other organs.

To doubt the operability of the invention, the Examiner has the initial burden to provide evidence to the contrary. It is well settled in the patent case law that a specification disclosure that contains a teaching of the manner and process of making and using the invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Further, the burden is on the Examiner to come forth with evidence to establish a prima facie case of non-enablement. *Ex parte Hitzeman*, 9 U.S.P.Q. 2d 1801, 1822 (Pat. Off. Bd. App. 1988); *In Re Armbruster*, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975); *In re Marzocchi*, 169 U.S.P.Q. at 370. While Applicants have provided ample evidence in the specification to show the methods disclosed in the present invention can successfully predict liver toxicity of test compounds, the Examiner has not provided any scientific evidence whatsoever to show that one skilled in the art would undergo undue experimentation to practice the present invention. Applicants therefore respectfully request the rejection be withdrawn.

The Examiner further contends that Table 1 does not comprise the identities of the metabolic pathways and that Applicants do not provide any disclosure as to whether the listed genes are specific for the metabolic pathways in the liver, or if said genes function specifically in the liver that are involved in hepatoxicity or liver toxicity. Applicants respectfully submit that in all the pending claims, no claim is drawn to a method of predicting the cellular pathways. Since the subject matter of cellular pathways is not claimed, the Examiner's

rejection is irrelevant to the pending claims. Applicants respectfully request that the rejection be withdrawn.

The Examiner further states that claims 105 and 124 recite specific disease pathologies that are predicted with the claimed methods. The Examiner then asserts that Applicants do not disclose whether the comparison is performed with normal liver tissues and liver tissues having the respective liver disease pathologies.

Applicants respectfully submit that claims 105 and 124 are dependent from claims 92 and 111, respectively. Both claims 92 and 111 recite a method of predicting for hepatoxicity of a test compound by preparing a gene expression profile from a liver tissue or liver cell sample exposed to the test compound. One of skill in the art would have recognized that the liver tissues or liver cells described in claims 92 and 111 are normal liver tissues before they are exposed to the test compound or known hepatotoxin. As an example, a hepatotoxin such as CCl_4 is known to induce hepatocellular damage or death. A gene expression profile derived from liver tissue exposed to CCl_4 carries the characteristic hepatocellular damage gene expression pattern. This pattern, in part, corresponds to the model of Tables 3I-3J. By comparing a gene expression profile of a liver tissue exposed to a test compound with a database of Tables 3I-3J produced from liver tissue exposed to CCl_4, one of skill in the art can predict whether the test agent induces hepatocellular damage or death. Accordingly, withdrawal of the pending rejection is requested.

Claim Rejections-35 U.S.C. § 112, First Paragraph (Lack of Written Description)

Claims 92-129 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention. More specifically, the Examiner contends that Claims 92-129 encompass "the genes in any one of Tables 3A-3S". However, Table 1 only discloses gene sequences with specific SEQ ID NOs. Therefore, the specification provides insufficient written description to support the genus encompassed by these claims.

Without acquiescing to the grounds of the Examiner's rejection, claims 60 and 80 have been amended to clarify that the genes are selected from the gene sequences listed in any one of Tables 3A-3S as correlated to the representative sequences of Table 1 and teachings of the specification. Applicants respectfully submit that the skilled artisan knows

the detailed chemical structure of the encompassed gene sequences as these sequences are all known sequences in the art and are specifically provided in the sequence listing submitted with the instant application. Furthermore, Applicants respectfully submit the facts in the present case differ significantly from those in the cited case law. *University of California v. Eli Lilly*, 43 U.S.P.Q. 2d 1398, describes the Federal Circuit's current view on patentability of cDNAs. Lilly cloned the rat insulin gene and described methods for isolating human cDNA based on the isolation of the rat insulin gene and known human insulin sequences. The court stated that the discovery of a single gene for rat insulin could not describe the entire group of vertebrate insulin DNA, or mammalian insulin DNA, as was claimed. *Amgen*, 18 U.S.P.Q. 2d 1016, concerned claims to a purified and isolated naturally occurring gene. The court held that a gene cannot be claimed until it is fully defined, *e.g.*, by determination of its nucleic acid sequence.

In contrast to the facts of *Lilly* and *Amgen*, the present invention includes methods of predicting for the hepatoxicity of a test compound by preparing a gene expression profile of at least ten genes from a liver tissue or liver cell sample exposed to the test compound. The claims are not directed to gene sequences that have not been disclosed as in *Lilly* and *Amgen*. Rather, the method of the present invention may be used to prepare gene expression profiles and compare those profiles to a database disclosed in the present application, wherein the nucleotide sequence for each and every gene in the database (one of Tables 3A-3S) is disclosed in the present application and is publicly available in GenBank. Applicants respectfully remind the Examiner that each "Identifier" in Tables 3A-3S corresponds to a GenBank Accession No. and SEQ ID NO. as correlated and set forth in Table 1.

As for the Examiner's concern of incorporation of essential material into the specification, Applicants respectfully submit that all of the gene sequences referred to by their GLGC ID in Tables 3A-3S are available from the GeneBank and thus are in public possession. Further, each sequence corresponding to each GenBank Accession No. is provided in the sequence listing which is part of the originally filed application (see Table 1). Therefore, Applicants have met the requirements of the first paragraph of Section 112 and respectfully request that this rejection be withdrawn.[1]

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1 Applicants note that sequences in GenBank are publicly available. Further, it has been long established that an Applicant need not provide in a patent application what is already known in the art. *Hybritech Inc. v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Claim Rejections-35 U.S.C. § 112, Second Paragraph

Claims 109 and 128 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, the Examiner contends that claims 109 and 108 recite the limitation of "the genes in Tables 3A-3S are rat genes" whereas Table 1 comprises sequences from R. norvegicus (rat), M. musculus (mouse), and unknown and the data in Tables 3A-3S are directed to the sequences listed in Table 1.

Applicants respectfully submit that there is no inconsistency in identifying the genes in Tables 3A-3S and Table 1. The assays described in the specification were all done in Sprague-Dawley rats and thus are rat genes. Although each of the genes in Tables 3A-3S correspond to a sequence listed in Table 1, Table 1 does not comprise only gene sequences from Tables 3A-3S. Therefore, Table 1 may comprise sequences from R. norvegicus (rat), M. musculus (mouse), or other species. Because claims 109 and 128, as amended, are not vague and indefinite, Applicants respectfully request withdrawal of this rejection.

Claim Rejections-35 U.S.C. § 102(b)

Claims 92, 106 and 111 are rejected under 35 U.S.C. 102(b) as being anticipated by Farr *et al.* (US Patent 5,811,231). According to the Examiner, Farr *et al.* describe a method for determining and characterizing the toxicity (predict) of a compound in terms of the damage it causes within the cell. The method of Farr *et al.* comprises exposing cells to a compound and creating an inducting profile (expression profile). As stated by the Examiner, Farr *et al.* also disclose a database of gene expression profiles comprising the GADD153, GADD45, HSP70, UGT, DNA pol, EH, CYP2E1, ALDH1 and ALDH2, IL-3, and IL-6 genes. The Examiner the asserts that the genes discloses by Farr *et al.* represents the at least 10 genes in Tables 3A-3S of the instant Application which are identified by the GLGC ID NOs: 351 (GADD45), 488 (CYP2E1), 1475 (HSP70), 1598 (GADD153), 2744 (UGT), 6615 (alcohol dehydrogenase), 14103 (EH), 14465 (DNA pol), and 20799 (IL3 and IL6). Applicants respectfully traverse.

For a reference to anticipate the claimed invention under 35 U.S.C. §102, the reference must describe the invention such that "each and every limitation is found either expressly or inherently" within it. *Transclean Corp. B. Bridgewood Services, Inc.*, 290 F.3d 1364, 1370, 62 USPQ2d 1865, 1869 (Fed. Cir. 2002) (citations omitted); see Manual of Patent Examining Procedure, section 2131 (8th ed. 2004) ("MPEP") ("to anticipate a claim,

the reference must teach every element of the claim").

Claims 92 and 111 recite in part "wherein said at least ten genes...in any one of Tables 3A-3S." Applicants submit that the 10 genes recited in the Office Action as having been disclosed in Farr *et al.* do not correspond to at least 10 genes from any one of Tables 3A-3S as required by the pending claims. As evidenced by the plain language of claims 92 and 111, the database as claimed in the instant methods comprises gene expression levels for "at least ten genes...in any one of Tables 3A-3S." [Emphasis added.] As such, the comparison step of claims 92 and 111 is to a set of genes from a single liver toxicity model of any one of Tables 3A-3S as each of these tables discloses a single liver toxicity model. In other words, the comparison step of claims 92 and 111 is not to a set of at least 10 genes randomly selected from different models. Respectfully, the 10 genes recited in the Office Action from Farr *et al.* do not correspond to at least 10 genes from any one of Tables 3A-3S as claimed. Accordingly, Farr *et al.* cannot anticipate any of the pending claims. The pending rejection under 35 U.S.C. § 102(b) should be withdrawn.

Claim Rejections-35 U.S.C. § 103(a)

Claims 92, 97-101, 111, and 116-120 are rejected under 35 U.S.C. §103(a) as being unpatentable over Farr et al. (US patent 5,811,231). Applicants respectfully traverse this rejection. Applicants first reiterate that in order for a reference to render a claim obvious under § 103, it must teach or suggest all of the elements of that claim. However, as described in the preceding section, Farr does not teach or suggest the at least 10 genes from "any one of Tables 3A-3S," as required by all of claims 92, 97-101, 111, and 116-120. No other reference was cited to correct this deficiency. Therefore, the Examiner has failed to provide a prima facie case of obviousness, and Applicants request the withdrawal of this rejection.

Claims 92, 107, 111 and 126 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231) in combination of Lashkari *et al.* (PNAS, Vol. 94, pages 13057-13062, 1997). This rejection is also respectfully traversed.

With respect to the primary reference Farr *et al.*, the Examiner is directed to the discussions of the §102 rejection presented above. As indicated, Farr *et al.* do not disclose or suggest that the at least 10 genes to be compared are selected from any one of Tables 3A-3S.

The other cited reference, Lashkari *et al.* do not provide what Farr lacks.

Lashkari is limited to a disclosure of gene expression patterns of the yeast genome. Lashkari *et al.* do not discuss any method remotely related to Applicant's claimed method of predicting for the hepatoxicity of a compound using liver tissues or liver cell samples, nor does it discuss databases comprising the gene expression levels derived from liver tissue or liver cell samples in any context.

Accordingly, even if these references were properly combined (which Applicants do not concede), the combination of Farr and Lashkari does not provide Applicant's claimed method predicting for the hepatoxicity of a compound with liver tissues or liver cell samples because neither reference discloses or suggests the important step of selecting the at least 10 genes from any one of Tables 3A-3S. Applicants respectfully request that the §103(a) rejection be withdrawn.

Conclusion

Applicant respectfully requests reconsideration of the subject application in view of the amendments to the claims and the above remarks. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this amendment, the Examiner is requested to contact the Applicant's undersigned representative.

If there are any fees due in connection with the filing of this amendment, please charge the fees to our Deposit Account No. 50-1283. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: 12-6-05

Respectfully submitted,
Cooley Godward LLP

By _____
Michael S. Tuscan
Registration No. 43,210

Cooley Godward LLP
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